SEQUENCE LISTING

<110> HARTMANN, ARNO
BRANDT, SILKE
RIEKE, ERWIN
SOBEL, CORNELIUS
LO, KIN-MING
WAY, JEFFREY C.
GILLIES, STEPHEN

<120> ERYTHROPOIETIN FORMS WITH IMPROVED PROPERTIES

<130> MERCK-2056

<140> 09/708,506
<141> 2000-11-09

<150> 60/164,855
<151> 1999-11-12

<160> 26

<170> PatentIn Ver. 2.1

<210> 1
<211> 514
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (8)..(505)
<223> Human EPO, DNA sequence modified but no change in protein sequence

<400> 1

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cccgggt gcc cca cca cgc ctc atc tgt gac agc cga gtg ctg gag agg   49
        Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
          1               5                  10

tac ctc ttg gag gcc aag gag gcc gag aat atc acg acc ggc tgt gct   97
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
 15                  20                  25                  30

gaa cac tgc agc ttg aat gag aac atc acc gtg cct gac acc aaa gtg   145
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
                 35                  40                  45

aat ttc tat gcc tgg aag agg atg gag gtt ggc cag cag gcc gta gaa   193
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
            50                  55                  60

gtg tgg cag ggc ctg gcc ctg ctg tcg gaa gct gtc ctg cgg ggc cag   241
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
        65                  70                  75

gcc ctg ttg gtc aac tct tcc cag ccg tgg gag ccc ctg caa ctg cat   289
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
     80                  85                  90

gtg gat aaa gcc gtg agt ggc ctt cgc agc ctc acc act ctg ctt cgg   337
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
 95                  100                 105                 110

gct ctg gga gcc cag aag gaa gcc atc tcc cct cca gat gcg gcc tca   385
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
```

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                115                 120                 125

gct gct ccc ctc cgc aca atc act gct gac act ttc cgc aaa ctc ttc   433
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
            130                 135                 140

cga gtc tac tcc aat ttc ctc cgg gga aag ctg aag ctg tac aca ggg   481
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
        145                 150                 155

gag gcc tgc cgg aca ggg gac aga tgactcgag                         514
Glu Ala Cys Arg Thr Gly Asp Arg
    160                 165


<210> 2
<211> 166
<212> PRT
<213> Homo sapiens

<400> 2
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
  1               5                  10                  15

Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
             20                  25                  30

Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
         35                  40                  45

Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
     50                  55                  60

Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
 65                  70                  75                  80

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
                 85                  90                  95

Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
            100                 105                 110

Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
        115                 120                 125

Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
    130                 135                 140

Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
145                 150                 155                 160

Cys Arg Thr Gly Asp Arg
                165


<210> 3
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 3
ccgggtgccc caccacgcct catctgtgac agccgagtgc tggagaggta cc          52
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<210> 4
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 4
tcttggaggc caaggaggcc gagaatatca cgaccggctg tgctgaaca 49

<210> 5
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 5
ctgcagcttg aatgagaaca tcaccgtgcc tgacaccaaa gtgaatttct at 52

<210> 6
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 6
gcctggaaga ggatggaggt tggccagcag gccgtagaag tgtggcag 48

D1 Cont

<210> 7
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 7
ggcctggccc tgctgtcgga agctgtcctg cggggccagg ccctgttggt c 51

<210> 8
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 8
aactcttccc agccgtggga gcccctgcaa ctgcatgtgg ataaagccg 49

<210> 9
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 9
tgagtggcct tcgcagcctc accactctgc ttcgggctct gggagcccag aa 52

<210> 10
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 10
ggaagccatc tcccctccag atgcggcctc agctgctccc ctccgcac 48

<210> 11
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 11
aatcactgct gacactttcc gcaaactctt ccgagtctac tccaatttcc tcc 53

<210> 12
<211> 59
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

D1 Cont

<400> 12
ggggaaagct gaagctgtac acaggggagg cctgccggac aggggacaga tgactcgag 59

<210> 13
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 13
tcttggaggc caaggaggcc gagcagatca cgaccggctg tgctgaaca 49

<210> 14
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 14
ctgcagcttg aatgagcaga tcaccgtgcc tgacaccaaa gtgaatttct at 52

<210> 15
<211> 49
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 15
cagtcttccc agccgtggga gcccctgcaa ctgcatgtgg ataaagccg 49

<210> 16
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 16
ggaagccatc tcccctccag atgcggccgc agctgctccc ctccgcac 48

<210> 17
<211> 232
<212> PRT
<213> Homo sapiens

<220>
<223> Human IgG1 Fc region-mature protein

<400> 17
Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

```
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230
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<210> 18
<211> 326
<212> PRT
<213> Homo sapiens

<220>
<223> Human IgG2 constant region (CH1, hinge, CH2, Ch3) - mature protein

<400> 18

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
  1               5                  10                  15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
             20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
         35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
     50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                 85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
        115                 120                 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220
```

```
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Lys
                325
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<210> 19
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 19
Ala Ala Ala Ala
1

<210> 20
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 20
Ala Ala Ala Ala Ala
1   5

<210> 21
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 21
Gly Gly Gly Gly
1

<210> 22
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 22
Gly Gly Gly Gly Gly
1 5

<210> 23
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 23
Gly Gly Gly Gly Gly Gly Gly
1 5

<210> 24
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<400> 24
Gly Gly Pro Gly Gly
1 5

<210> 25
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

D! cont
<400> 25
Gly Gly Gly Gly Ser
1 5

<210> 26
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Linker

<220>
<223> This linker sequence may encompass five to
twenty five amino acids is groups of (GGGGS)

<400> 26
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25